

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of :  
Ulf TILSTAM et al.  
Serial No.: 09/471,040 : Group Art Unit: 1623  
Filed: December 23, 1999 : Examiner: Elli PESELEV

For: PROCESS FOR THE PRODUCTION OF FLUDARABINE-PHOSPHATE  
LITHIUM, SODIUM, POTASSIUM, CALCIUM AND MAGNESIUM SALTS  
AND PURIFICATION PROCESS FOR THE PRODUCTION OF  
FLUDARABINE-PHOSPHATE AND FLUDARABINE-PHOSPHATE WITH A  
PURITY OF AT LEAST 99.5%

**DECLARATION UNDER 37 C.F.R. §1.132**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450  
Sir:

Dr. Stefan Scholz being duly warned, declares that:

I am an employee of the assignee, Bayer Schering Pharma AG,  
Berlin, Germany.

I have performed or supervised the experiments reported below.  
My CV is attached.

I have read the office action in this application dated December 11,  
2007 and the references cited therein, USP's 5,110,919 (Butler) and  
5,506,352 (Blumbers).

I understand the examiner to allege that 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate can be purified to 99.5% purity using the procedures reported in Butler, column 5, lines 44 – 67 and column 6, lines 1 – 18. I was asked to employ the latter processes in an effort to purify 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate to the extent possible. As described below, when it was quickly determined that the Butler processes could not be applied as reported to purify 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate to a satisfactory degree, I then designed alternative conditions in an effort to optimize the results obtainable using the Butler procedures. This work is described below. In all cases, the highest purity obtainable was on the order of about 92% only.

#### Experiment 1

The procedure of Example 1 of USP 5,506,352 (Butler) was reproduced, as follows, except 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine was used instead of 9-( $\beta$ -D-arabinofuranosyl)adenine and except for the attempts to improve the purity of the produced 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate as mentioned below.

#### Preparation of the corresponding phosphate using Butler's procedure.

The needed amount of phosphorous oxychloride ( $\text{POCl}_3$ ) was calculated using the corresponding formula given at col. 4, lines 52 – 53 of Butler.

49g of 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine (purity of 95.7%) is charged to a 2-l-round-bottom three-neck flask. Triethyl phosphate (959 g) is charged to the same flask and a nitrogen blanket of 2 l per minute is applied to the flask (used to exclude atmospheric moisture while cooling the contents). The mixture is agitated and cooled to between  $-15^\circ\text{C}$ . and  $-20^\circ\text{C}$ . The number of grams of  $\text{POCl}_3$  as calculated=32,9 g is mixed under nitrogen with 133 g of dichloromethane. The  $\text{POCl}_3/\text{CH}_2\text{Cl}_2$  solution is dropped into the inerted 2-l-round-bottom three neck flask maintaining the temperature of the reaction mixture between  $-15^\circ\text{C}$ . and  $-20^\circ\text{C}$ . with cooling. The last of the  $\text{POCl}_3/\text{CH}_2\text{Cl}_2$  solution is rinsed into the reactor with 10 g of dichloromethane. Agitation is continued throughout. However, after 163 hours of reaction, the in-process assay does not show less than 3.0 % of starting 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine but 13.1 % instead. Thereafter, in order to increase the yield, two additional portions  $\text{POCl}_3/\text{CH}_2\text{Cl}_2$  [2.54 ml  $\text{POCl}_3$  in 13 ml  $\text{CH}_2\text{Cl}_2$  and 5.1 ml  $\text{POCl}_3$  in 26 ml  $\text{CH}_2\text{Cl}_2$ ] were added. However, after 267 hours of total reaction time the in-process assay does not show less than 3.0 % of starting 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine but 6.56 % instead. No further increase in the amount of phosphate product resulted. No precipitation was observed.

#### Propylene oxide based purification of Butler.

Then, as in Butler, the mixture is poured into an agitated mixture of 504 g of demineralized water and 150 g of ice with cooling to maintain the temperature at  $15\pm 2^\circ\text{C}$ . The mixture is allowed to warm to  $20^\circ\text{C}$ . to  $22^\circ\text{C}$ . when the addition is complete and agitated for 60 minutes. Dichloromethane (1.08 Kg) is then added and the mixture agitated vigorously for 30 minutes. The agitator is turned off, the layers are allowed to separate for 30 minutes, and the dichloromethane layer is drained. Another addition of dichloromethane, 282 g, is made. The mixture is agitated vigorously for 30 minutes, the layers are allowed to separate, and the dichloromethane layer is drained. The aqueous layer is filtered through a G4-frit (10-16 $\mu\text{m}$ ) to remove any particulates and the filter is washed with 40 mL of demineralized water that is added to the filtrate. In a 4-l-round-bottom three-neck flask, propylene oxide (44.1 g) and 2.102 Kg of anhydrous ethanol are charged, agitated vigorously, and the temperature of the mixture held at  $20^\circ\text{C}$ . to  $25^\circ\text{C}$ . The aqueous product solution from the 2-l-round-bottom three-neck flask is added to the propylene oxide/ethanol solution with vigorous agitation while holding the temperature between  $20^\circ\text{C}$ . to  $25^\circ\text{C}$  within 50 minutes. The agitation is continued throughout.

However, after 24 hours no precipitation resulted. No isolation was possible because the solution was completely clear. Even after additional 24 hours of stirring at 20 °C. to 25 °C no crystals were produced.

In an effort to enhance crystallization, the temperature was lowered to 0 – 5 °C and stirred for 24 hours. 9-(β-D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate crystallized in a yield of 1g (1.5% of theory) and having a purity of 81.6%.

HPLC: stationary phase Chemcosorb ODS-H, 5μm 150x4.6 mm, mobile phase method A: methanol/water (cont. 10mmol/L KH<sub>2</sub>PO<sub>4</sub>) 60+940 volumes, mobile phase method B: methanol/water (cont. 10mmol/L KH<sub>2</sub>PO<sub>4</sub>) 200+800 volumes, flow 1.0 mL/min, room temp., sample solution: 1 mg/mL water, inj. vol. 2 μL, detector: UV 260 nm, purity determination by sum of impurities obtained from method A and B

#### Ammonium hydroxide purification according to Butler

The procedure reported by Butler could not be performed due to the too small amount of product obtained by the foregoing procedures.

#### Experiment 2

The procedure of Example 1 of USP 5,506,352 (Butler) was reproduced, as follows, except 9-(β-D-arabinofuranosyl)-2-fluoro-adenine was used instead of 9-(β-D-arabinofuranosyl)adenine and except for the attempts to improve the purity of the produced 9-(β-D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate as mentioned below.

#### Preparation of the corresponding phosphate using Butler's procedure.

The needed amount of phosphorous oxychloride (POCl<sub>3</sub>) was calculated using the corresponding formula given at col. 4, lines 52 – 53 of Butler.

47.95g of 9-(β-D-arabinofuranosyl)-2-fluoro-adenine (purity of 95.7%) is charged to a 2-l-round-bottom three-neck flask. Triethyl phosphate (939 g) is charged to the same flask and a nitrogen blanket of 2 l per minute is applied to the flask (used to exclude atmospheric moisture while cooling the contents). The mixture is agitated and cooled to between -15 °C. and -20 °C. The number of grams of POCl<sub>3</sub> as calculated=32.2 g is mixed under nitrogen with 130 g of dichloromethane. The POCl<sub>3</sub>/CH<sub>2</sub>Cl<sub>2</sub> solution is dropped into the inerted 2-l-round-bottom three neck flask maintaining the temperature of the reaction mixture between -15 °C. and -20 °C. with cooling. The last of the POCl<sub>3</sub>/CH<sub>2</sub>Cl<sub>2</sub> solution is rinsed into the reactor with 10 g of dichloromethane. Agitation is continued throughout. However, after 168 hours of reaction, the in-process assay does not show less than 3.0 % of starting 9-(β-D-arabinofuranosyl)-2-fluoro-adenine but 7.6 % instead. No precipitation was observed.

#### Propylene oxide based purification of Butler.

Then, as in Butler, the mixture is poured into an agitated mixture of 490 g of demineralized water and 150 g of ice with cooling to maintain the temperature at 15±2

°C. The mixture is allowed to warm to 21 °C. to 22 °C. when the addition is complete and agitated for 60 minutes. Dichloromethane (1.08 Kg) is then added and the mixture agitated vigorously for 30 minutes. The agitator is turned off, the layers are allowed to separate for 30 minutes, and the dichloromethane layer is drained. Another addition of dichloromethane, 283 g, is made. The mixture is agitated vigorously for 30 minutes, the layers are allowed to separate, and the dichloromethane layer is drained. The aqueous layer is filtered through a G4-frit (10-16µm) to remove any particulates and the filter is washed with 40 mL of demineralized water that is added to the filtrate. In a 4-l-round-bottom three-neck flask, propylene oxide (42.2 g) and 1.975 Kg of anhydrous ethanol are charged, agitated vigorously, and the temperature of the mixture held at 20 °C. to 25 °C. The aqueous product solution from the 2-l-round-bottom three-neck flask is added to the propylene oxide/ethanol solution with vigorous agitation while holding the temperature between 20 °C. to 25 °C within 40 minutes. The agitation is continued throughout. However, after 36 hours no precipitation resulted. No isolation was possible because the solution was completely clear. Even after additional 24 hours of stirring at 20 °C. to 25 °C no crystals were produced.

In an effort to enhance crystallization, the temperature was lowered to 0 – 5 °C and stirred for 24 hours. 9-(β-D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate crystallized in a yield of 1g. In an effort to enhance the yield, the resulting solution was reduced in volume to 50% using a rotation evaporator. This produced 41 g (67 % of theory) of 9-(β-D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate with a purity of 91.9%. The purity determination is as described in experiment 1.

#### Ammonium hydroxide purification according to Butler

40 g of 9-(β-D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate is charged to an inerted 4-l-round-bottom three-neck flask followed by 480 g of demineralized water. The agitator is started and the temperature of the slurry is adjusted to between 20 °C. to 25 °C. Ammonium hydroxide, 28% solution, is added until the pH of the mixture is 6.03 (consumption: 13ml) maintaining the temperature below 25 °C. The agitation is continued until solution is essentially complete. The solution is filtered through a G4-frit (10-16µm), followed by a rinse with 80 g of demineralized water.

While maintaining the temperature of the mixture between 20 °C. and 25 °C with cooling, the pH of the aqueous product mixture is adjusted to 2.49 using filtered 36% aqueous hydrochloric acid solution (consumption: 6.2ml). Within 50 minutes 450 ml of filtered anhydrous ethanol is charged to the stirring aqueous product mixture. As jellification occurs after 6 hours, agitation is continued and the temperature is held at 20 °C for 72 hours. The still jelly-like product was then isolated by vacuum filtration (suction filter) and the product washed with two 10ml-portions of anhydrous ethanol. The solid is dried in a vacuum tray drier at 40±5 °C and 10-20 mbar vacuum until analyses by Karl Fischer shows less than 7% water and residual solvent analysis shows less than 1.0% ethanol. The yield of 9-(β-D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate was 11.3 g (28% of theory) having a purity of 92.2%.

### Conclusion

As can be seen, using the identical conditions and procedures of Butler, it was not possible to obtain 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate in a purity greater than 92.2%, even after trying reasonable variations of the process designed to optimize the purity and amount of product and despite the fact that the starting 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine had a purity of 95.7%. Thus, yet another attempt (Experiment 3) was made to use the Butler processes to obtain the highest purity of 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate product.

### Experiment 3

The procedure of Example 1 of USP 5,506,352 (Butler) was reproduced, as follows, except 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine was used instead of 9-( $\beta$ -D-arabinofuranosyl)adenine and except for the attempts to improve the purity of the produced 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate as mentioned below.

#### Preparation of the corresponding phosphate using Butler's procedure.

The needed amount of phosphorous oxychloride ( $\text{POCl}_3$ ) was calculated using the corresponding formula given at col. 4, lines 52 – 53 of Butler.

46.0 g of 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine (using an even higher purity of 97.2%) is charged to a 2-l-round-bottom three-neck flask. Triethyl phosphate (900 g) is charged to the same flask and a nitrogen blanket of 2 l per minute is applied to the flask (used to exclude atmospheric moisture while cooling the contents). The mixture is agitated and cooled to between  $-15^\circ\text{C}$ . and  $-20^\circ\text{C}$ . The number of grams of  $\text{POCl}_3$  as calculated=30.9 g is mixed under nitrogen with 125 g of dichloromethane. The  $\text{POCl}_3/\text{CH}_2\text{Cl}_2$  solution is dropped into the inerted 2-l-round-bottom three neck flask maintaining the temperature of the reaction mixture between  $-15^\circ\text{C}$ . and  $-20^\circ\text{C}$ . with cooling. The last of the  $\text{POCl}_3/\text{CH}_2\text{Cl}_2$  solution is rinsed into the reactor with 10 g of dichloromethane. Agitation is continued throughout and the temperature raised to  $-5^\circ\text{C}$  and  $-10^\circ\text{C}$  (instead of the lower temperature stated in Butler). The use of the higher temperature produced a good reaction. The in-process assay shows less than 3.0 % (1.66% after 120 hours) of starting 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine. The mentioned dichloromethane extraction produced a precipitated product.

#### Propylene oxide based purification of Butler.

Then, as in Butler, the mixture is poured into an agitated mixture of 307 g of demineralized water and 307 g of ice with cooling to maintain the temperature at  $15\pm 2^\circ\text{C}$ . The mixture is allowed to warm to  $21^\circ\text{C}$ . to  $22^\circ\text{C}$  when the addition is complete and agitated for 60 minutes. Dichloromethane (1.016 Kg) is then added and the mixture agitated vigorously for 30 minutes. The agitator is turned off, the layers are allowed to separate for 30 minutes, and the dichloromethane layer is drained. Another addition of

dichloromethane, 265 g, is made. The mixture is agitated vigorously for 30 minutes, the layers are allowed to separate, and the dichloromethane layer is drained. Before the aqueous layer could be filtered, as in Butler, 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate precipitated out of the aqueous solution. In a 4-l-round-bottom three neck flask, propylene oxide (41.4 g) and 1.974 Kg of anhydrous ethanol are charged, agitated vigorously, and the temperature of the mixture held at 20 °C. to 25 °C. The aqueous suspension from the 2-l-round-bottom three-neck flask is added to the propylene oxide/ethanol solution with vigorous agitation while holding the temperature between 20 °C. to 25 °C. The agitation is continued for 24 hours. However, only a gelatinous product could be obtained from which the product could not be isolated using the Butler procedure. Thus, the mixture was extracted 5 times with dichloromethane and the dichloromethane layer drained. After stirring of the aqueous suspension for 19 hours at 20 °C to 23 °C, a slimy product was isolated, which after analysis was established as being 24 g (41 % of theory) of 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate with a purity of 91.4%.

The purity determination is as described in experiment 1.

#### Ammonium hydroxide purification according to Butler

24 g of 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate is charged to an inerted 2-l-round-bottom three-neck flask followed by 290 g of demineralized water. The agitator is started and the temperature of the slurry is adjusted to between 20 °C. to 25 °C. Ammonium hydroxide, 28% solution, is added until the pH of the mixture is 6.0 maintaining the temperature below 25 °C (consumption: 8ml). The agitation is continued until solution is essentially complete. The solution is filtered through a G4-frit (10-16 $\mu$ m), followed by a rinse with 48 g of demineralized water.

While maintaining the temperature of the mixture between 20 °C. and 25 °C with cooling, the pH of the aqueous product mixture is adjusted to 2.5 using filtered 37% aqueous hydrochloric acid solution (consumption: 3.7ml). Within 60 minutes, 214g of filtered anhydrous ethanol is added to the stirred solution. As jellification occurs, agitation is continued and the temperature is held between 15 °C. and 25 °C for 48 hours. The still jelly-like product was isolated from the slurry by vacuum filtration (suction filter), washed with one 190ml portion of anhydrous ethanol and dried as described before. The yield was 7g (30 % of theory) of 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate, having a purity of 90.7%.

These experiments show that the Butler process cannot be used to obtain a purity of 9-( $\beta$ -D-arabinofuranosyl)-2-fluoro-adenine-5'-phosphate of 99.5%.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18

of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

26.05.2008  
Date

Dr. Stefan Scholz  
Dr. Stefan Scholz

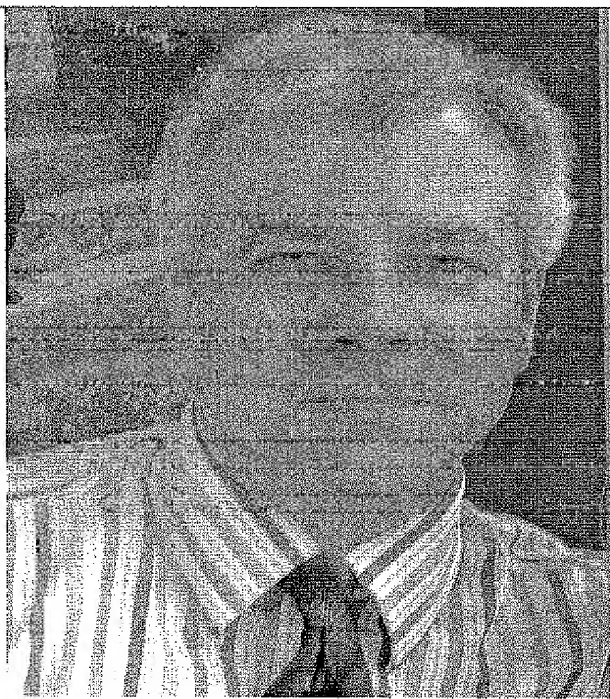
# CV

## Content:

1. Status sheet
  2. Educational history
  3. Job history
  4. Additional information
-



**1. Status sheet*****Strictly confidential – only for internal use***

<b>Last /First name:</b>	<b>Year of birth*:</b> 1958	
<b>Scholz, Dr. Stefan</b>		
<b>Nationality*:</b> German	<b>Hired</b> (month/year): 02/ 87	
<b><u>Short profile</u></b>  Leader with focus on <ul style="list-style-type: none"> <li>• the delivery of results</li> <li>• effective leadership and teambuilding</li> <li>• the successful implementation of innovative processes</li> </ul>		

**Current Position:**

<b>Name of position</b>	Head of Pilot Plant SH
<b>Date of appointment</b>	1995
<b>Local title / rank</b>	Abteilungsleiter
<b>Organizational Unit</b>	Global Chemical Development (GChD)
<b>Location</b>	Berlin
<b>Manager(s) reporting to</b>	Dr. W. Kuebler
<b>Number of direct / total reports</b>	8/ 47

\*According to legal requirements in your country you may leave this field blank.

**2. Educational history (prior to career entry as well as during your professional career):**

Year	Degree
2004	Schering Corporate University, Cranfield, UK
1985 – 1987	Post Doctorate, Colorado State University, Co, USA
1982 – 1985	Ph. D. in Chemistry, Technical University Berlin
1977 – 1982	Study of Chemistry, Diploma, Technical University Berlin
1977	Abitur

**3. Job history (internal / external):**

Name of position	Start year – end year (please begin with recent position)	Rank (in your country)	Title (in your country)	Number of reports		Company / Country
				direct	total	
Head of Pilot Plant SH	1995 - recent	Abteilungsleiter	Abteilungsleiter SHB	8	47	Schering AG, Berlin, Germany

**Job description**

Managed development, scale up and transfer of new processes for commercial API manufacturing with current budget of 12.5 Mio €. Supported supply chain by small scale production with a turnover of 150 Mio €/a. Supervised staff of 8, mainly chemists/ engineers.

**Major achievements**

- As manufacturer of Iloprost, Fludara and Sulproston fully responsible for regulatory compliance. Started with the clear instruction "Ready for FDA- inspection within 3 years". Re-engineered all relevant processes in the plant to reach compliance. Developed and implemented GMP policies with impact on the whole GChD environment. Result: FDA pre-approval inspection successfully completed [1996 – 1999; PAI in 2000].
- Led a sub-team of the project "Pool-Model" (with shop floor personal from both plants, works council and Human Resources) and successfully negotiated major aspects, resulting in a flexible assignment of chemical workers to both plants according to workload requirements.
- Implemented the continuous improvement program 'step' as the first department within GChD [1999 – recent], resulting in better effectiveness of staff / processes and major cost savings (e.g. 300.000 € annually by energy savings; highest no. of batches per worker).
- Encouraged a working environment where diverse opinions are freely expressed and valued as well as successfully created an atmosphere of identification and satisfaction with one's own work to achieve optimum performance, even in challenging situations. Best result within GChD in the employee leadership assessment 2005 (180° feedback on leadership performance).
- Schering's delegate in a group of experts from companies of the *Verbandes Forschender Arzneimittelhersteller e. V. (VFA)*. Discussed the chapter "Cleaning Validation" of the ICH-guideline Q7a "GMP for APIs". Justified 10 times higher limits for Cleaning Validation in the manufacture of APIs in comparison to pharmaceutical production. Justification successfully implemented in Scherings IMS Directive avoiding much higher cleaning efforts in the future.
- Described the future strategic needs to facilitate synthesis and handling of high potency active pharmaceutical ingredients (HPAI) in GChD. Carried out a benchmark and finalized a concept for future upgrading of GChD capabilities in technology, know-how as well as management of these HPAI- projects [Project leader 2004 – 2006].
- Contributed GMP- and production know-how to the successful establishment of a production concept for epothonine, one of the most challenging API projects in Schering's history, resulting in the avoidance of early investments while safeguarding expected supplies.



**4. Additional information****Fluency of language skills:**

(4 = basic knowledge; 3 = working knowledge; 2 = negotiation level; 1 = native speaker level)

German: 1, English: 2, French: 4

**Geographic mobility:**☒ mobile – within country or region☐ mobile – internationally☐ not mobile**Job-relevant significant training, licenses or certifications, memberships, special skills, awards, recognitions, relevant publications etc.****significant training**

1. Certificate of Attendance on "Finance for managers" at Ashridge Business School, UK (2005)
2. Successful completion of "Leadership for Growth and Success" at Cranfield School of Management, UK (2004)
3. Certificate of Attendance on "Managerial Effectiveness Program" at Management Zentrum St. Gallen, CH (F. Malik, 2002)

**relevant publications**

1. Begründung von Grenzwerten bei Reinigungsvalidierungen in der Wirkstoffherstellung, P. Mungenast, F. Adam, A. Littek, W. Kausler, A. Fromm, S. Barth, S. Roch, E. Reinholz, S. Scholz, C. Althoff, Pharm. Ind. 66, Nr. 9, 1142 – 1145 (2004)
2. Synthesis of 14 $\beta$ - H- antiprogestines, A. Cleve, G. Neef, E. Ottow, S. Scholz, W. Schwede, Tetrahedron 51 (19), 5563 – 72 (1995)
3. Synthesis of 14, 17- bridged 11 $\beta$ - arylsteroids, S. Scholz, H. Hofmeister, G. Neef, E. Ottow, C. Scheidges, R. Wiechert, Liebigs Ann. Chem. 151-8 (1989)
4. An efficient enantioselective synthesis of the carbapenam- 2- one system. An approach to (+)- thienamycin and related carbapenems, A. I. Meyers, T. J. Sowin, S. Scholz, Y. Ueda, Tetrahedron Lett. 28 (43), 5103-6 (1987)
5. Terpenes and terpene derivatives. XXI. Synthesis of rac- 4, 5- dihydro-  $\beta$ - curcumene- 4, 5- diol, P. Weyerstahl, H. Marschall- Weyerstahl, S. Scholz, Liebigs Ann. Chem. 11, 1013-14 (1987)
6. Isolation and synthesis of compounds from the essential oil of Helichrysum italicum, P. Weyerstahl, H. Marschall- Weyerstahl, M. Weihrauch, N. Meier, E. Manteuffel, J. Leimner, S. Scholz, Prog. Essent. Oils, 16th, 177-95 (1986)
7. Terpenes and terpene derivatives. XIX. Selective epoxidation of rac-  $\beta$ - curcumene. Synthesis of 1- (4- methyl- 1, 4- cyclohexadien- 1- yl) ethanone, P. Weyerstahl, H. Marschall- Weyerstahl, S. Scholz, Liebigs Ann. Chem. (7), 1248-54 (1986)
8. Terpenes and terpene derivatives. XVIII. Preparation of rac-  $\gamma$ - curcumene, P. Weyerstahl, H. Marschall- Weyerstahl, S. Scholz, Liebigs Ann. Chem. (6), 1021-9 (1986)
9. Friedel- Crafts reaction of 2- methylfuran with saturated and  $\alpha$ ,  $\beta$ - unsaturated acid anhydrides, S. Scholz, H. Marschall- Weyerstahl, P. Weyerstahl, Liebigs Ann. Chem. (10), 1935-50 (1985)

**relevant patents**

1. Preparation of Hydroxyalkanamides, S. Scholz, M. Harre, H. Vidic, G. Neef, G. Kirsch, Ger. Offen. DE 4214895 A1 (1993)
2. Preparation of Androstanone derivatives as drugs, S. Scholz, G. Neef, E. Ottow, W. Elger, S. Beier, K. Chwalisz, Eur. Pat. Appl. EP 360369 A1 (1990)
3. Preparation of 13- Alkyl- 11 $\beta$ - phenylgonanes as antigestagens and antiglucocorticoids, S. Scholz, E. Ottow, G. Neef, W. Elger, S. Beier, K. Chwalisz, Ger. Offen. DE 3822770 A1 (1990)
4. Preparation and testing of 11 $\beta$ - phenyl- 4, 9, 15- estratriene- 3- ones as antigestagens and antiglucocorticoids, E. Ottow, H. Hofmeister, S. Scholz, G. Neef, W. Elger, S. Beier, K. Chwalisz, Eur. Pat. Appl. EP 299913 A1 (1989)